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Chapter 2

ELECTROMAGNETIC INTERACTION BETWEEN ENVIRONMENTAL FIELDS AND LIVING SYSTEMS DETERMINES HEALTH AND WELL-BEING

Dimitris J. Panagopoulos*
University of Athens, Department of Biology, Athens, Greece
Radiation and Environmental Biophysics Research Centre, Athens, Greece

ABSTRACT

In the present chapter we present data showing the electric nature of both our natural environment and the living organisms and how the inevitable interaction between the two, determines health and well-being. We first give a brief theoretical background of electromagnetic fields (EMFs) and waves and delineate the differences between natural and man-made electromagnetic radiation. Apart from other differences, while man-made radiation produced by oscillation circuits is polarized, natural radiation produced by atomic events is not. We describe the electromagnetic nature of our natural environment on Earth, i.e. the terrestrial electric and magnetic fields, the natural radiation from the sun and the stars, the cosmic microwaves and the natural radioactivity. We note that all living organisms on Earth live in harmony with these natural fields and types of radiation as long as these fields are within normal levels and are not disturbed by changes, usually in solar activity. We then describe the electrical nature of all living organisms as this is determined by the electrical properties of the cell membranes, the circadian biological clock, the endogenous electric currents within cells and tissues, and the intracellular ionic oscillations. We explain how the periodicity of our natural environment mainly determined by the periodical movement of the earth around its axis and around the sun, implies the periodical function of the suprahiasmatic nuclei (SCN) - a group of neurons located above the optic chiasm - which constitute the central circadian biological clock in mammals. We discuss the probable connection between the central biological clock with the endogenous electric oscillations within cells and organs constituting the "peripheral clocks", and how the central clock controls the function of peripheral ones in the heart, the brain, and all parts of the living body by

* Correspondence: 1) Dr. Dimitris Panagopoulos, Department of Biology, University of Athens, Panepistimiopolis, 15784, Athens, Greece. Fax: +30210 7274742, Phone: +30210 7274273. E-mail: dpanagop@biol.uoa.gr, 2) Dr. Dimitris Panagopoulos, Radiation and Environmental Biophysics Research Centre, 79 Ch. Trikoupi str., 10681 Athens, Greece., E-mail: dpanagop@biophysics.gr

electrical and chemical signals. We explain how cellular/tissue functions are initiated and controlled by endogenous (intracellular/trans-cellular) weak electric currents consisting of directed free ion flows through the cytoplasm and the plasma membrane, and the connection of these currents with the function of the circadian biological clock. We present experimental data showing that the endogenous electric currents and the corresponding functions they control can be easily varied by externally applied electric or magnetic fields of similar or even significantly smaller intensities than those generating the endogenous currents. We present two possible ways by which external EMFs like those produced by human technology can distort the physiological endogenous electric currents and the corresponding biological/physiological functions: a) By direct interference between the external and the endogenous fields and, b) By alteration of the intracellular ionic concentrations (i.e. by changing the number of electric current carriers within the cells) after irregular gating of electrosensitive ion-channels on the cell membranes. Finally, we discuss how maintenance of this delicate electromagnetic equilibrium between living organisms and their natural environment, determines health and well-being, and how its disturbance will inevitably lead sooner or later to health effects.

1. INTRODUCTION

For millions of years since the beginning of their existence, all living organisms live within a natural electromagnetic environment determined by the earth's electric and magnetic fields, the sun's electromagnetic activity, cosmic ionizing and non-ionizing radiation (including the "cosmic microwaves"), and terrestrial radioactivity consisting of γ radiation and charged particles. These natural electromagnetic field/radiation sources generate a continuous flow of electromagnetic energy within which all living creatures exist.

This natural electromagnetic environment with frequencies ranging from infrared to gamma rays (with the exception of the static terrestrial fields and the cosmic microwaves) has more or less a constant intensity level most of the time and living organisms have adapted to this stable electromagnetic environment for millions of years. Nevertheless, during "magnetic storms" arising from increased sun activity, variations on the order of ~20% in the normal levels of natural fields take place. During these variations that usually last a few days a considerable increase in health problems takes place in humans and all living organisms on earth.

During the last century and especially during the last decades, man-made EMFs (like those associated with power lines) and wireless communications radiation at frequencies below the low limit of infrared have appeared with constantly increasing levels at very high rates. These unnatural (artificial) EMFs are quiet different from the natural ones basically due to the fact that they are polarized, varying, usually modulated, and generated in a continuous mode by electric/electronic oscillation circuits. These artificial EMFs add to the natural environmental ones increasing the exposure of living creatures to EMFs and constituting what is called "electromagnetic pollution".

The technological evolution connected with the production and use of these artificial polarized electromagnetic fields is tremendous and can be used either for the benefit or the destruction of humankind and the environment. An increasing number of biological and consequent health effects are being reported to be connected with these artificial fields. These effects range from simple changes in the normal cellular rates, to reproductive collapses and DNA damage with following consequences (cancer, cell death, degenerative neural deceases, heritable mutations etc) (Goodman et al 1995; Phillips et al 2009; Johansson 2009;

Panagopoulos 2011). Epidemiological studies show a connection between exposure to man-made electromagnetic fields of different frequencies and different types of cancer in human population (Wertheimer and Leeper 1979; Savitz et al 1988; Feychting and Ahlbom 1993; 1994; 1995; Coleman et al 1989; Draper et al 2005; Carlo and Jenrow 2000; Hallberg and Johansson 2002; Hardell et al 2007; 2009; Hardell and Carlberg 2009; Khurana et al 2009).

Some still insist that they see nothing of these, that environmental man-made electromagnetic fields cannot cause any biological/health effects as long as they don't cause tissue heating, and that the reported effects simply do not exist. Could that ever be possible?

All living organisms consist of cells and have a precise and delicate electromagnetic nature. All functions at cellular, tissue, and organ level are controlled by physiological endogenous electric fields like the trans-membrane electric fields, and corresponding weak transient endogenous electric currents, like the intracellular electric currents originating from cytoplasmic voltage differences due to corresponding differences in the concentrations of mobile ions within cells. Intracellular electric currents are found to control cell growth, proliferation, differentiation, etc, while corresponding electric currents within tissues involving hundreds/thousands of cells, control embryonic development, wound healing, or tissue regeneration.

Electromagnetic oscillations generated in the brain of all mammals by the SCN - specialized neurons constituting their central circadian biological clock - seem to control physiological functions, health and vitality. Moreover, "spontaneous" intracellular ionic oscillations in the extremely low frequency (ELF: 0-300 Hz) range within every part of the body seem to constitute the peripheral clocks controlled by the central biological clock. Similar biological clocks and intracellular oscillations exist within all living organisms.

This internal subtle electromagnetic network within all living bodies will inevitably interact with any other electromagnetic field - natural or manmade - in their environment. This interaction will cause changes (distortion) in the form, intensity, frequency and direction of the subtle natural endogenous electromagnetic fields/currents, and this in turn will distort the corresponding cellular/biological functions controlled by the specific endogenous fields.

If the external fields are of a constant form (like the terrestrial static electric and magnetic fields) the cells adapt to them more easily. But if they change constantly and unexpectedly (as during magnetic storms or as with most types of man-made fields) the cells cannot adapt. This is when alterations in cellular functions leading to biological changes and health effects originate.

Therefore it is obvious that under normal conditions an electromagnetic equilibrium occurs between living organisms and natural environment. If this equilibrium is disturbed, physiological functions will be disrupted also. In the present chapter we explain how the electromagnetic nature of all living organisms interacts with the electromagnetic natural environment to maintain health and well-being and how unnatural electromagnetic radiation/fields can disrupt this equilibrium.

2. Electromagnetic Fields and Waves

2.1. Maxwell Equations

Classical electromagnetic theory is synopsized in the following four Maxwell's equations:

1. Electric field flow through a closed surface (S) is proportional to the net electric charge (q) included within this surface:

$$\oint_S \vec{E} \cdot \vec{u}_N dS = \frac{q}{\varepsilon_o} \tag{1}$$

2. Magnetic field flow through a closed surface (*S*) is zero:

$$\oint_S \vec{B} \cdot \vec{u}_N dS = 0 \tag{2}$$

3. Electric field circulation along a closed line (*l*) (in other words, the magnetically induced electromotive force - voltage - *V* along a closed conductor *l*), equals the temporal variation rate of the magnetic field flow through the surface (*S*) included within that closed line:

$$\oint_l \vec{E} \cdot d\vec{l} = -\frac{d}{dt}\int_S \vec{B} \cdot \vec{u}_N dS \tag{3}$$

4. Magnetic field circulation along a closed line (*l*) (in other words, the induced magnetic field along a closed line *l*) is proportional to the total electric current (the transport current *I*, plus the displacement current) through the surface (*S*) included within that closed line:

$$\oint_l \vec{B} \cdot d\vec{l} = \mu_o I + \varepsilon_o \mu_o \frac{d}{dt}\int_S \vec{E} \cdot \vec{u}_N dS \tag{4}$$

where: $\vec{E}$, $\vec{B}$ are the intensities of the electric and magnetic field respectively, $\vec{u}_N$ is the unit vector vertically to the surface *S*, $d\vec{l}$ is an incremental length along the closed conductor *l*, $\varepsilon_o = 8.854\times10^{-12}$ $C^2/N{\cdot}m^2$ = $1/4\pi K_e$ is the electric permittivity (dielectric constant) of vacuum, and $\mu_o=4\pi{\cdot}10^{-7}$ V·sec/A·m $=4\pi{\cdot} K_m$ is the magnetic permeability of vacuum.

The above form of Maxwell's equations is valid for the vacuum or the air.

Equations (3) and (4) will be more useful to us in a differential form, which is correspondingly:

$$\vec{\nabla} \times \vec{E} = -\frac{\vartheta \vec{B}}{\vartheta t} \tag{5}$$

and $\vec{\nabla} \times \vec{B} = \mu_o \vec{j} + \varepsilon_o \mu_o \dfrac{\partial \vec{E}}{\partial t}$ (6)

where, $\vec{j}$ is the electric current surface density.

The first equation, also known as Gauss' law for the electric field, declares that the electric field is proportional to the net electric charge that generates it.

The second equation, also known as Gauss' law for the magnetic field, declares that there can be no single magnetic poles but any magnetic pole is always in pair with an equal opposite one. Thereby, the amount of magnetic flow leaving a closed surface containing a magnet (with two opposite poles) will always equal the amount entering the same closed surface.

According to the third equation, also known as Faraday-Henry law, a temporally varying magnetic field induces an electric field, the intensity of which is proportional to the variation rate of the magnetic field intensity.

According to the fourth equation, also known as Ampere-Maxwell law, an electric current *I*, or/and a temporally varying electric field induce a magnetic field, the intensity of which is linearly dependant to the electric current intensity plus the variation rate of the electric field intensity.

2.2. Plane Electromagnetic Waves

The generation of an electromagnetic wave, presumes time-varying electric and magnetic fields connected to each other in a way that the one induces the other in a degree proportional to the rate of temporal variation, according to Maxwell's third and fourth laws.

If we consider an oscillating electric field parallel to *Y* axis and an oscillating magnetic field parallel to *Z* axis in a rectangular coordinate system (*X*, *Y*, *Z*), then from equations (3) and (4) [or better from (5) and (6) correspondingly] after operations, it comes that:

$$\frac{\partial^2 E}{\partial t^2} = \frac{1}{\varepsilon_o \mu_o} \frac{\partial^2 E}{\partial x^2} \tag{7}$$

and: $$\frac{\partial^2 B}{\partial t^2} = \frac{1}{\varepsilon_o \mu_o} \frac{\partial^2 B}{\partial x^2} \tag{8}$$

Comparing eq. (7), (8), with the Wave Equation:

$$\frac{\partial^2 \xi}{\partial t^2} = u^2 \frac{\partial^2 \xi}{\partial x^2} \qquad (9),$$

(where ξ is a disturbance, transmitted in the $\vec{x}$ direction with a velocity $\vec{u}$), it follows that the oscillating electric and magnetic fields in Eqs. (7), (8), are transmitted in the direction of *X* axis (vertically to both the electric and the magnetic fields) with a velocity:

$$c = \frac{1}{\sqrt{\varepsilon_o \mu_o}} \tag{10}$$

The magnitude of this velocity (which is also the velocity of light since light is also electromagnetic radiation) in the vacuum or in the air, was found experimentally by Heinrich R. Hertz, in 1888 and it is the transmission velocity, of every time-varying electromagnetic field, in the vacuum or in the air:

$$c = \frac{1}{\sqrt{\varepsilon_o \mu_o}} = 2.9979\times10^8 \text{ m/sec} \cong 3\times10^8 \text{ m/sec.}$$

Then the value of the constant μ_o (magnetic permeability of the vacuum), was arbitrarily defined: $\mu_o=4\pi\cdot10^{-7}$ V·sec/A·m = $4\pi\cdot K_m$ and according to this, the value of ε_o , (dielectric constant or electric permittivity of the vacuum), was calculated by Eq. (10): $\varepsilon_o = 8.854\times10^{-12}$ $C^2/N\cdot m^2 = 1/4\pi K_e$

The described electromagnetic waves are called plane or linearly polarized electromagnetic waves, since both the electric and the magnetic components oscillate on certain planes vertical to each other. The plane of the *E*-component is considered as the plane of the electromagnetic wave.

If, in addition, the electric and the magnetic fields vary harmonically with a frequency $\nu = \omega/2\pi$, then they produce harmonic waves (in the $\vec{x}$ direction) with a wavelength: $\lambda = 2\pi/k_w$. In this case:

$$E = E_o \sin k_w(x-ct) = E_o \sin (k_w x-\omega t) \tag{11}$$

and $$B = B_o \sin k_w(x-ct) = B_o \sin (k_w x-\omega t) \tag{12}$$

where: $\omega = 2\pi\nu = k_w \cdot c$, is the circular frequency and k_w $(=2\pi/\lambda)$ is called the wavenumber. [The product of the frequency times the wavelength is the velocity of the electromagnetic wave (and of any wave): $c = \lambda\cdot\nu$]

From equations (10), (11), (12) and because $\frac{\partial E}{\partial x} = -\frac{\partial B}{\partial t}$, [deriving from eq. (5)], we finally get:

$$E = cB \tag{13}$$

Equation (13), refers to the magnitudes of the vectors $\vec{E}$, $\vec{B}$, declaring that the two fields/components of the electromagnetic wave, are at every moment, in phase with each-other (in the case of harmonic plane waves).

A combination of linearly polarized electromagnetic waves with equal amplitudes for each field and with certain phase difference, gives circularly polarized electromagnetic waves, or elliptically polarized, if the corresponding amplitudes are different. [Circularly polarized, are the three-phase Power Transmission Line Fields away from the lines. Near and under the lines these fields are elliptically polarized].

2.3. Energy of Electromagnetic Waves

The Energy Density of an electric field (in the vacuum or in the air), is given by the equation:

$$W_e = \frac{1}{2}\varepsilon_o E^2 \tag{14}$$

Eq. (14), also gives the energy density related to the electric component of an electromagnetic wave (not necessarily plane one).

Correspondingly, the energy density for magnetic field, (or for the magnetic component of an electromagnetic wave), is:

$$W_m = \frac{1}{2\mu_o} B^2 \tag{15}$$

From equations (10), (13), (14), (15), we get (for a plane, harmonic wave):

$$W_m = W_e = \frac{1}{2} \varepsilon_o E^2 \tag{16}$$

Thus, the total energy density (in J/m^3) of a plane, harmonic electromagnetic wave (in the vacuum or in the air), is:

$$W = W_e + W_m = \varepsilon_o E^2 \tag{17}$$

2.4. Intensity of Electromagnetic Waves, (Power Density)

The Intensity $\vec{J}$ of the electromagnetic wave, (power per unit surface area), is equal to the energy density times the wave velocity $\vec{c}$:

$$\vec{J} = \vec{c}\, W \tag{18}$$

It has the same direction as the velocity of the wave, and is called "Poynting vector".

For a plane, harmonic wave in the vacuum or in the air,

$$\vec{J} = \vec{c}\, \varepsilon_o E^2 \tag{19}$$

From eq. (13), (19), it comes that:

$$\vec{J} = c^2\, \varepsilon_o\, \vec{E} \times \vec{B} \tag{20}$$

or $$\vec{J} = \frac{1}{\mu_o}\, \vec{E} \times \vec{B} \tag{21}$$

If we know the intensity J of a plane, harmonic wave, then according to Eqs. (21) and (13), the magnitude of its electric component in the vacuum or in the air, is calculated by the equation:

$$E^2 = J\sqrt{\frac{\mu_o}{\varepsilon_o}} \quad (22)$$

where $\sqrt{\frac{\mu_o}{\varepsilon_o}}$ = 376.87 Ω ≅ 377 Ω, is called the "wave impedance". Hence:

$$E^2 \cong J \times 377 \quad (23)$$

(E in V/m, J in W/m^2)

Correspondingly, the magnitude of the magnetic component in the vacuum or in the air, satisfies the equation:

$$B^2 = \frac{\mu_o}{c} J \quad (24)$$

or $$B^2 \cong J \times 4.2 \times 10^{-15} \quad (25)$$

(B in T, J in W/m^2)

The $\vec{B}$ vector, represents the intensity of the magnetic field within a certain medium and is usually called also, Magnetic Induction, or Magnetic Flux Density.

Frequently in textbooks we also see the $\vec{H}$ vector, which represents the intensity of the magnetic field regardless of the medium.

The two vectors are connected by the relation:

$$\vec{B} = \mu\mu_o \vec{H} \quad (26)$$

(H, in A/m in SI)

where: μ is the relative magnetic permeability of the medium. [In the vacuum or in the air, $\mu = 1$. Within biological matter it is similarly $\mu \cong 1$].

From Eqs. (13), (26) we get for the plane, harmonic wave in the vacuum or in the air:

$$E/H = \sqrt{\frac{\mu_o}{\varepsilon_o}} \approx 377\ \Omega \quad (27)$$

The relation between the different units of $\vec{H}$ and $\vec{B}$, (in the vacuum or in the air), is:

1G ($\vec{B}$) = 1 Oe ($\vec{H}$) = 10^{-4} T ($\vec{B}$) = 79.58 A/m ($\vec{H}$)

3. NATURAL AND MAN-MADE ELECTROMAGNETIC FIELDS IN THE TERRESTRIAL ENVIRONMENT

3.1. Natural EMFs on Earth

For millions of years throughout the course of evolution, all living organisms in the terrestrial environment have been constantly exposed to terrestrial static electric and magnetic fields of average intensities ~130 V/m and ~0.5 G respectively. Variations in the intensity of the terrestrial magnetic field on the order of ±0.1 G during "magnetic storms" or "geomagnetic pulsations" mainly due to changes in solar activity are connected with increased rates of animal (and human) health incidents, including nervous and psychic diseases, hypertensive crises, heart attacks, cerebral accidents, and (consequently) mortality (Dubrov 1978; Presman 1977). Increase in solar activity leads to corresponding increases in the intensity of visible, ultraviolet, gamma, and meson solar radiation, increase in ionization of the earth's atmosphere, intensity of atmospheric discharges, and increases in the earth's magnetic and electric fields (Presman 1977). It is interesting to note that even human female fertility periodic variations seem to follow variations in the earth's magnetic field due to lunar periodic variations determined by the lunar month (~28 days).

Terrestrial Electric Field: On the earth's surface there is a natural electric field of constant polarity (static) with an average intensity ~130 V/m, and vertical direction from the atmosphere towards the earth. Its intensity varies with latitude. It is minimum at the equator and at the poles and becomes maximum at intermediate latitudes. Moreover, its intensity diminishes exponentially with height from the sea surface (at 9 km above sea its intensity is ~5 V/m). This terrestrial electric field displays annual and diurnal periodicity in its intensity following the corresponding variation in atmospheric conductance which in turn depends on storm periodicity. That means that during winter, the intensity of terrestrial electric field at a certain place is larger than during summer. Intensity variations between different places follow the variations of storm frequency (Pressman 1977).

Terrestrial Magnetic Field: This is also of constant polarity. Magnetic poles are close but opposite to the corresponding geographical poles. In every place the terrestrial magnetic field has a vertical and a horizontal component. At the magnetic poles the horizontal component becomes almost zero while at the magnetic equator the vertical component becomes almost zero. The average resultant intensity of the terrestrial magnetic field is ~0.5 G. In every place there are periodic variations as well as non-periodic disturbances (changes) in its intensity on the order of ±0.1 G, called "magnetic storms" which result from variations in solar activity (variation in the number of solar "spots" and "flares") (Dubrov 1978).

Cosmic Microwave Radiation: More than five decades ago it was discovered that microwave radiation of a broad spectrum (10 MHz – 10GHz) and of cosmic origin, reaches the earth's surface and can be detected (Presman 1977). Its intensity is very low ($\sim 10^{-17}$ $mW/cm^2/MHz$), and probably represents radiation of higher frequencies above the low limit of infrared ($\sim 3\times10^{11}$ Hz) which reaches on Earth with decreased frequency because of the universal expansion.

Other types of Natural Electromagnetic Radiation on Earth: Within the different types of natural electromagnetic radiation on Earth we should also refer to the infrared, visible and ultraviolet radiation from the sun and the stars, and the natural gamma radiation of cosmic origin and radioactive minerals on Earth (uranium, radium, strontium, etc). Nevertheless, in the present chapter we shall refer mainly to the natural and artificial EMFs with frequencies below the low limit of infrared.

3.2. Artificial EMFs on Earth

At the same time, modern man is constantly exposed to artificial (man-made) EMFs with frequencies ranging from ELF to radio-frequencies (RF)/microwaves which reach closer and closer to the low limit of infrared.

One of the most common EMF-exposures in modern human environment since the beginning of the twentieth century and even earlier, is the exposure to the fields associated with electric power generation, transport, and consumption. Electric energy is produced in the form of 50-60 Hz alternating three-phase electric current and transported to residential areas by high-voltage power lines of usually hundreds of kV in order to minimize thermal looses. Within residential areas the high voltage is transformed to 220-230 V prior to distribution for residential usage. Close to transformer substations or under power lines the magnetic field intensity may reach values between 0.5 and 1 G, while the electric field may reach values up to 10 kV/m.

A large number of biological effects due to magnetic field exposure have been reported (Goodman et al 1995). In addition, several epidemiological studies during the last thirty years have shown a connection between exposure to power line or transformer magnetic fields and cancer (Wertheimer and Leeper 1979; Savitz et al 1988; Feychting and Ahlbom 1993; 1994; 1995; Coleman et al 1989; Draper et al 2005). This connection has been shown for magnetic field intensities down to 2 mG (Feychting and Ahlbom 1994), or distances from power lines up to 600 m (Draper et al 2005). Another epidemiological study points to the electric and not to the magnetic component of the power line fields as having a connection with child leukemia for intensities down to 10 V/m, (Coghill et al 1996).

The current Exposure Limits for 50 Hz Magnetic Fields, (for *rms* magnetic field intensities), are 1G (24h exposure) for the general population and 10 G (exposure of a few hours during the working day) for occupational exposure. The corresponding 50 Hz Electric Field Exposure Limits are 5 kV/m and 10 kV/m (ICNIRP 1998; IRPA 1990). These values are even higher than those found under power lines or close to transformers.

In addition to the 50-60 Hz EMFs, modern man as well as animals and plants are exposed since the early decades of the twentieth century to constantly increasing levels of manmade RF/microwave radiation from radio/television station antennas and radars. In addition, and especially during the last twenty years, modern man is exposed to a "sea" of microwave radiation from wireless telecommunications, wireless internet connections (Wi-Fi), satellites etc. The type of radiation emitted by these technological applications is of varying intensity, polarized, including simultaneously two or more different, usually varying, frequencies (a carrier frequency plus a modulation frequency, and recently several different carrier and modulation frequencies and a pulse repetition frequency which is also usually variable).

The strongest and most commonly used microwave emitters in human proximate daily environment are the GSM (Global System for Mobile Telecommunications) mobile phones (also called "cell phones") with a maximum output power 1-2 W, usually carried and used with no precaution in contact with the human body/head even by small children. These devices emit complicated, constantly and unpredictably changing signals which include a more and more complicated modulation in order to carry more and more information i.e. not only voice (GSM), but also video, music, internet , etc (3G, 4G, Tetra). Still, while the use of mobile phones is voluntary, human exposure to similar radiation emitted by the mobile telephony base station antennas which are installed everywhere within residential and working areas, although of usually smaller intensity (at a distance of several tenths or hundreds of meters) than that of a mobile phone in contact, is continuous (24 h daily) and involuntary. If additionally we take into account exposures from cordless domestic phones (DECT), wireless internet (Wi-Fi) which tends to be installed everywhere in schools, public places, stores, coffee places, homes, etc., which all emit similar types of microwave radiation, it follows that exposure to microwave radiation of modern wireless communications is another main type of human/environmental EMF-exposure.

Therefore modern man and his environment are constantly and increasingly exposed to artificial types of EMFs/radiation constantly and unpredictably varying, polarized, and unknown to living organisms throughout development.

A large and constantly increasing number of biological/health effects are attributed in our day to human and animal exposure to these artificial EMFs. Among them, the most serious is genotoxicity (DNA damage) which may lead to cell death, reproductive declines, functional disorders, cancer induction, heritable mutations, etc. (Phillips et al 2009; Johansson 2009; Panagopoulos 2011).

Since all living organisms on Earth live in harmony with the natural terrestrial EMFs for millions of years, but increased health problems appear whenever these natural fields vary mainly due to variations in solar activity as explained before, it seems that living organisms have the natural ability to adapt to constant values of natural static electric and magnetic fields, while variations in these fields generate health problems.

Living organisms seem to perceive EMFs as environmental stress factors (Panagopoulos 2011) and they can adapt more easily to them when their parameters are kept constant or vary slightly. In addition, living organisms do not seem to have defense mechanisms against large variations of natural EMFs, and moreover do not have defense against unnatural (man-made) EMFs which are mostly not static but varying. This is probably the reason why cells in response to manmade EMF-exposure activate heat shock genes much more rapidly and at a much higher rate than for heat itself (Weisbrot 2003).

3.3. Differences between Natural and Artificial Electromagnetic Radiation

All time-varying EMFs produce electromagnetic waves propagating with the velocity of light and with the frequencies of the EMFs which generate them.

Natural electromagnetic radiation is generated (and absorbed) by matter discontinuously by single atomic/molecular events and in particular, excitation and de-excitation of molecules (infrared), atomic electrons (visible, ultraviolet, x-rays), and atomic nuclei (gamma rays). Therefore, it is transmitted also discontinuously in the form of discrete wave-packets called "quanta" or "photons" and the energy of each photon, is given by Planck's equation:

$$W_{photon} = h \cdot \nu \tag{28}$$

where: $h = 6.625 \times 10^{-34}$ J·sec, is the Planck's constant and ν the photon's frequency.

Artificial (manmade) electromagnetic waves are generated in electrical/electronic oscillation circuits by induced (forced) oscillations of electric charge (free electrons) and transmitted by antennas connected to the oscillation circuits. Thus they are (usually linearly) polarized with the plane of polarization determined by the geometry of the oscillation circuit.

Moreover, artificial electromagnetic waves, have frequencies below the low limit of infrared, ($\nu < 3\times10^{11}$ Hz), and they can be emitted continuously, (in the form of continuous waves), by the oscillation circuits.

In contrast, electromagnetic waves emitted by natural sources, (and by some artificial ones, like the electric light), are not polarized, since every source of radiation/light, consists of many elementary sources, i.e. radiating atoms or molecules, randomly polarized, so that actually there is no polarization. In addition, natural electromagnetic waves, have frequencies ranging from the low limit of infrared up to gamma rays, (3×10^{11} Hz $\leq \nu \leq 3\times10^{22}$ Hz). [Cosmic microwave radiation which seemingly constitutes an exception to this rule, probably is, as already explained, radiation of higher frequencies (most likely above the low limit of infrared) which reaches the earth with decreased frequency because of the universal expansion].

Polarized waves can produce interference effects and induce coherent forced-vibrations on charged/polar molecules within a medium, whereas non-polarized, cannot. This is probably the reason why polarized waves, (like man-made EMFs), seem to be in many cases more bioactive than non-polarized radiation of equal or even higher frequency and intensity (as is natural light).

4. Interaction between Man-Made EMFs/Radiation and Living Matter

4.1. A General Hypothesis for the Type of Interaction

The interaction mechanisms of (natural) infrared, visible, ultraviolet and ionizing electromagnetic radiation with matter (biological and inanimate) are more or less known since the early decades of the 20th century. Here we are mostly concerned with the interaction of manmade EMFs - frequencies below infrared - and of natural static electric and magnetic fields with biological matter. The mechanisms of this interaction are still under investigation.

As already explained, natural terrestrial electric and magnetic fields are mainly of static nature and thus exert constant forces on charged/polar bio-molecules resulting to a slight polarization of the biological matter towards the direction of the terrestrial electric field (towards the centre of the earth) and vertically to the level determined by the terrestrial magnetic field and the velocity of these charged bio-molecules which are free to move as are the mobile ions (Laplace/Lorenz forces). Within normal intensity values of the terrestrial static fields, living organisms can tolerate these natural electric and magnetic forces. [Polarization of biological tissue by external fields is discussed more extensively in section 6.1.].

Natural electromagnetic radiation, in the form of photons of different polarization and with frequencies ranging from infrared to gamma rays, is generated and absorbed by matter through excitation/de-excitation phenomena as already mentioned.

Artificial oscillating EMFs with frequencies ranging from a few Hz to $\sim10^{10}$ Hz reaching more and more closely to the low limit of infrared ($\sim3\times10^{11}$ Hz), produce polarized electromagnetic waves which cannot induce molecular or atomic excitation or ionization but are able to induce forced-vibrations in the charged/polar molecules of living matter.

Let us examine what happens when a polarized, non-ionizing electromagnetic oscillation - wave - passes through a mass of polar and charged molecules such as those composing biological tissue.

The electromagnetic wave will induce a forced-oscillation on each of these particles that it meets and will transfer to each of them a tiny part of its energy. This induced oscillation will be most intense on the free particles which carry a net electric charge such as the free (mobile) ions that exist in large concentrations in all types of cells or extracellular biological tissue determining practically all cellular/biological functions (Alberts et al 1994; Panagopoulos and Margaritis 2003). The induced oscillation will be much weaker or even totally negligible on the polar biological macromolecules and the water molecules that do not have a net charge and additionally are usually bound chemically to other molecules.

After each such event of interaction between the wave and a charged or polar particle, the remaining wave continues on its way through the tissue possibly scattered by a tiny angle and reduced by a tiny amount in its amplitude/intensity. After large numbers of such events, depending on the tissue's mass, density, and the number of polar/charged molecules, the remaining wave, if any, leaves the tissue as a scattered wave of reduced amplitude/intensity (Panagopoulos et al 2013).

The density of energy W_e (energy per unit volume) of an electric field E within a medium with relative permittivity ε, is given - in respect to Eq. (14) - by the equation:

$$W_e = \frac{1}{2}\,\varepsilon\varepsilon_o E^2 \tag{29}$$

The total energy density W_{em} of a plane, harmonic electromagnetic wave (as those usually produced by "Thomson" circuits) accounting also for the magnetic component, is in respect to Eq (17):

$$W_{em} = \varepsilon\varepsilon_o E^2 \tag{30}$$

Thus according to Eq. (29) and (30), when the amplitude/intensity E of the oscillating field or wave is decreasing after interaction with the charged/polar molecules of a medium, its energy density decreases as well. That means that a part of its energy per unit volume is transferred to the charged/polar molecules of the medium.

In general, the amount of energy absorbed by a certain amount of matter determines the degree of interaction between exposed matter and exposing radiation. But in the case of biological matter this is not as simple. Biological tissue is a much more complicated and organized form of matter compared to inanimate. The degree of interaction does not necessarily determine the biological effect. Even if we could accurately estimate the amount of absorbed energy by a whole organ (e.g. by measuring an increase in temperature if any), the biological effect depends on which specific bio-molecule(s) will absorb a certain amount of energy and this is impossible to discern. Some bio-molecules may get damaged while others may not by the same amount of radiation energy. Thus, in the case of biological matter, the amount of absorbed energy alone is not enough to determine the biological effect (Panagopoulos et al 2013).

For example, when radiation is absorbed by lipids the damage will most likely be less than when the same amount of energy is absorbed by enzymes and potentially even smaller than when absorbed by nucleic acids - especially DNA. The situation becomes even more complicated in case that the biological effects are indirect as they are in most cases. For example, damage in the DNA may be due not to the energy absorbed directly by the DNA molecule but due to a conformational change in a membrane protein leading to irregular alteration of intracellular ionic concentrations (as described in section 6.2) and this in turn giving a signal for a cascade of intracellular events causing irregular release of free radicals or DNases which finally damage DNA (indirect effect).

In conclusion, in regard to the interaction between radiation and living matter (especially man-made electromagnetic but not only), the amount of absorbed radiation energy alone, does not determine the biological effect.

For this, dosimetry based on the Specific Absorption Rate (*SAR*) (defined as the amount of radiation power absorbed by the unit mass of biological tissue) might not be a credible measure to determine the biological activity of EMFs (Panagopoulos et al 2013).

4.2. The Energy Absorbed by Biological Molecules during Exposure to Man-Made EMFs Is Normally Well Below the Thermal Level

Electromagnetic radiation absorbed by matter does not always cause measurable temperature increases. Heating naturally occurs when the absorbed radiation has a frequency above the lower limit of infrared (~3×10^{11} Hz) (Panagopoulos and Margaritis 2003). Man-made microwave radiation used in modern telecommunications and other applications with frequencies 10^8-10^{10} Hz cannot directly cause measurable temperature increases in biological tissue unless it is of large enough intensity (well above 1 mW/cm^2) as for example in the case of a microwave oven that operates at about 10^3 W. Radiation of even lower frequency would need to be of even larger power/intensity to produce thermal effects. Usual microwave intensities in modern human environment (mainly due to mobile telephony handsets and base station antennas, Wi-Fi, and radio-television station antennas) are between 0.01 μW/cm^2 and 100 μW/cm^2 (Panagopoulos et al 2013).

Man-made radiation that has neither the frequency nor the intensity to cause tissue heating (thermal effects), is absorbed - as explained above - in much smaller quantities by inducing forced-oscillations on polar molecules and free charges such as the free ions within all living cells. These forced-oscillations are superimposed on the thermal vibration of the same particles increasing - theoretically - their thermal energy. But as we shall demonstrate, the energy of the oscillations induced by external EMFs at environmental exposure levels (intensities) is normally millions of times smaller than the average thermal energy *kT* of the molecules within biological tissue, and thus it does not produce measurable temperature increases (Panagopoulos et al 2013).

Although these induced oscillations (with kinetic energy usually thousands/millions of times lower than the average thermal energy) normally do not add to tissue temperature, they can still cause severe biological alterations (such as DNA damage) without heating the tissue (Panagopoulos 2011). These are called “non-thermal effects” and if not properly equilibrated by the organism’s immune and other compensatory systems, they may very well result in health effects (Goodman 1995; Johansson 2009; Carlo 1998; Carlo and Jenrow 2000; Carlo and Thibodeaux 2001).

Let us estimate the amount of energy lost by a plane harmonic electromagnetic wave after an interaction with a single free ion within biological tissue. The total energy acquired by the charged free particle due to the forced-oscillation induced by the wave is the total energy of the harmonic oscillation:

$$\in_i = \frac{1}{2} m_i u_o^2 \tag{31}$$

where, m_i is the ion mass which in the case of a Na^+ ion, is $m_i \cong 3.8\times10^{-26}$ kg. u_o is the particle's maximum velocity of the forced-oscillation assumed to be equal to $\cong$ 0.25 m/s, which is the drift velocity of Na^+ ions along an open trans-membrane sodium channel, as calculated from patch-clamp ionic current measurements through open channels (Neher and Sakmann 1992; Stryer 1996; Panagopoulos et al 2000).

From Eq. (31) after substituting the values of the parameters, we get that the energy absorbed by a single ion due to the interaction with the electromagnetic wave, is on the order of: $\in_i \approx 10^{-27}$ J.

Considering that the concentration of free ions within cells is on the order of 1 ion per nm^3 (Alberts et al 1994) and a typical cell volume up to 10^3 μm^3, a single cell contains about 10^{12} free ions and thus it will absorb about $10^{12}\times10^{-27}$ J = 10^{-15} J. A human body of average size consisting of $\sim10^{14}$ cells, will absorb about $10^{14}\times10^{-15} = 10^{-1}$ J. For waves emitted by a supposed unidirectional antenna operating with 1 W (= 1 J/sec) output power, (thereby transmitting energy 1 J per sec) it takes about 10 human bodies in sequence in order to be totally absorbed, according to the above mechanism, which seems a reasonable result.

Certainly, except for the energy absorbed by mobile ions within biological tissue, there will be additional energy absorption by the water dipoles and the charged or polar macromolecules like proteins, lipids, or nucleic acids, which will also be forced to oscillate by the applied field. While we can have a rough estimation as shown above for the energy absorbed by mobile ions, we are unable to estimate much smaller amounts of energy absorbed by water or charged/polar biological macromolecules. These smaller amounts of energy may be of decisive importance for the biological effect (Panagopoulos et al 2013).

Let us compare the velocity and kinetic energy acquired by a free ion within biological tissue, due to an external EMF, with the thermal velocity and energy of such a particle:

The maximum velocity of the ion's induced vibration is assumed to be, $u_o \cong 0.25$ m/s as explained already, and the corresponding maximum kinetic energy given by Eq (31), is calculated to have a value: $\in_i \approx 10^{-27}$ J.

This ion possesses also an additional average velocity u_{kT}, due to its thermal energy, given by the equation:

$$u_{kT} = \sqrt{\frac{3kT}{m_i}} \tag{32}$$

where T=310 ^oK (the temperature of the human body at 37^{o}C), $k = 1.381\times10^{-23}$ $J{\cdot}K^{-1}$ the Boltzmann's constant, and m_i the ion's mass ($m_i \cong 3.8\times10^{-26}$ kg for Na^+ ions) (Panagopoulos et al. 2000; 2002; 2013).

Eq. (32) derives from the equation for the average kinetic energy of a single-atom molecule/free ion due to thermal motion (Mandl 1988):

$$\in_{kT} = \frac{1}{2} m_i\, u_{kT}^{\ 2} = \frac{3}{2} kT \tag{33}$$

From Eqs. (32) and (33) respectively we get: $u_{kT} \cong 0.58\times10^3$ m/s, and $\in_{kT} \cong 6.4\times10^{-21}$ J.

Comparing the values of the above two different velocities/energies we find that, the velocity acquired by a free ion within biological tissue due to an environmental EMF is normally about 2.3×10^3 ($\cong \frac{u_{kT}}{u_o}$) times smaller than its thermal velocity, and its kinetic energy $\in_i = \frac{1}{2} m_i\, u_o^2$ induced by the environmental EMF is about 5.3×10^6 times smaller than the average thermal energy $\frac{3}{2} kT$ of such a particle.

Thereby, we have shown that oscillations induced on biological molecules by environmental EMFs do not usually contribute to the tissue temperature, except if these fields were millions of times more powerful, as for example the fields within a microwave oven operating at about 1000 W and focusing all of its radiating power within its cavity, in contrast to a mobile phone (~ 0.1-1 W) or even a mobile telephony base station antenna (~ 10-100 W) radiating (and distributing their energy) in all directions within wide angles. This is the reason why initially it was believed by scientists and authorities that environmental EMFs could not induce any biological effect (Adair 1991a). Even though some scientists still express skepticism regarding the existence of non-thermal effects (Verschaeve et al 2010), there is already a large and constantly increasing number of studies indicating that environmental man-made EMFs can produce severe biological alterations such as DNA damage without heating the biological tissue (Panagopoulos and Margaritis 2008; Panagopoulos 2011; 2012; Johansson 2009; Goodman et al 1995; Carpenter and Livstone 1968; Kwee et al 1998; Velizarov et al 1999). This can take place through non-thermal mechanisms that involve direct changes in intracellular ionic concentrations or changes in enzymatic activity (Panagopoulos et al 2000; 2002; Liboff and McLeod 1988; Lednev 1991).

5. Physiological Endogenous Electric Fields in Cells and Tissues Practically Control All Cellular/Biological Functions

5.1. Trans-Membrane Electric Field

All membranes in living cells have a voltage difference between their external and internal surfaces called “resting membrane potential” with resultant strong electric field on the order of 10^7 V/m across the membrane, with the internal always negative in regard to the external. The membrane potential is mainly generated by unequal distributions of free ions between the internal and the external sides of the membrane aqueous solutions. This refers both to the plasma membranes surrounding the whole cell and the membranes of intracellular organelles like the mitochondria, endoplasmic reticulum, etc. When stimulated, some types of cells respond with short potential changes on their plasma membrane resting potential and revert to normal value again. These transient potential changes are called “action potentials” and are mostly found in nerve, muscle, and sensory cells. In this way (by generation of action potentials) information is transmitted between different parts of a living body through electrical signals in the form of transmitted changes in membrane potentials, which convert into chemical signals to pass from the one adjacent cell to the next, reconvert into electrical ones, and so on.

All cell membranes are lipid bilayers with polar external and internal surfaces and hydrophobic interior, forming a mosaic structure with membrane proteins. Some of these proteins called "trans-membrane proteins" penetrate completely the lipid bilayer forming channels through which polar/charged molecules can pass.

On both sides of every cell membrane, there are free ions, (mainly K^+, Na^+, Cl^-, Ca^{+2} etc.), which: a) control the cell volume, by generating osmotic forces which are responsible for the entrance or exit of water, b) play an important role in a plethora of metabolic cell processes/signal transduction processes, c) create the strong electric field between the two sides of the cell membrane. Actually, these ions are not really "free" but they are weakly and transiently bound to water dipoles. Nevertheless it is known that when they pass through the pores of the membrane channels they are dehydrated (Leuchtag 1992; 1994; Miller 2000) meaning that these ions have the ability to jump or flow between different water dipoles. These ions are also called, "mobile ions".

Mobile ("free") ions play a particularly important role in cell function. They move in and out of the cell membranes through trans-membrane protein channels of specific diameter, different for each type of ion. The channel walls are constructed from several trans-membrane parallel a-helices forming the channel's pore between them when the channel is in its open state. A specific type of channels are the "voltage-gated" or "electro-sensitive" ones, which are cation channels. These channels change between open and closed state when their "voltage-sensors" receive an electrostatic force after a change in the membrane potential of about 30mV (Bezanilla et al 1982; Liman et al 1991). Similarly there exist "ligand-gated" channels responding to chemical signals in the form of specific molecules (ligands) that bind to specific sites of the channel to induce gating, and "mechanically-gated" channels changing between open and closed state by mechanical pressure depending on the concentration of ions at the channel site.

The voltage sensors of the electro-sensitive channels, are four symmetrically arranged, transmembrane, positively charged a-helices, each one designated S4, (Noda et al 1986; Stuhmer et al 1989).

Membrane potentials were originally studied in the giant axons of the squid and other types of nerve and muscle fiber cells (Hodgkin and Huxley 1952). A more recent method is based on measuring equilibrium concentrations of ions between the external and internal sides of the membrane using charged dyes that bind to specific ions and performing fluorescence or absorption measurements (Neumcke 1983). After determining the concentrations of ions on both sides of the membrane, the trans-membrane voltage (membrane potential) is calculated by the *Nernst* Equation (34). This gives the potential difference across the plasma membrane, under equilibrium conditions, due to a particular type of ion:

$$\Psi_o - \Psi_i = -\frac{RT}{zF_c} ln\frac{C_o}{C_i} \tag{34}$$

where: Ψ_o, Ψ_i are the electrical potential on the external and internal surface of the membrane respectively, R is the gas constant, T is the Absolute Temperature (in °K), z is the ion's electric charge in electrons (the ion's valence), F_c is the Faraday constant, and C_o, C_i are the concentrations of a certain type of ion on the external and internal side of the membrane respectively at equilibrium, in other words, when the net flux of this ion, is zero.

The total electrical potential difference across the membrane, is the sum of the contributions from all the existing types of ions, restoring the final balance between osmotic and electrical forces.

Ion flux through cell membranes is caused by forces due to concentration and voltage gradients, between the two sides of the membrane. Under equilibrium conditions, the net ion flux through the membrane is zero and the membrane has a voltage difference ("resting membrane potential") $\Delta\Psi = \Psi_o - \Psi_i$ between its external and internal surface, varying between 20 and 200 mV in animal cells, with the internal always negative in relation to the external (Baker et al 1962; Hille 1992; Hodgkin and Huxley 1952; Alberts et al 1994).

The intensity $E_m = \Delta\Psi / s$ of the transmembrane electric field, assuming an average membrane width $s \sim 100$ A° = 10^{-8} m and $\Delta\Psi \sim 100$ mV = 0.1 V, has a value on the order of 10^7 V/m as already mentioned.

The membrane electric field is, as also stated already, mainly generated by the unequal distribution of mobile ions in the external and internal sides of the membranes, with the majority of positive ions at the external side. The "leak" channels of K^+ and Na^+ ions, play a crucial role, in cooperation with the K^+ - $N\alpha^+$ pump (K^+ - $N\alpha^+$ ATPase), while other electrogenic pumps contribute to a smaller degree, (Hille 1992; Stryer 1996). It is also the majority of negative charged lipids, on the inner surface of the lipid bilayer, in all membranes, and the majority of fixed anions in this side that contribute to the generation of the trans-membrane potential (Honig et al 1986; Neumke 1983; Alberts et al. 1994). In any case, the existence of the trans-membrane electric field is maintained by active transport of ions, since without the contribution of the electrogenic ion pumps, only a passive diffusion of ions through the membrane would not be enough to maintain the potential difference. The K^+ - $N\alpha^+$ ATPase transports by energy (ATP) consumption more Na^+ ions outside of a cell than K^+ ions inside at a ratio of 3/2, contributing in this way to a more negative cell interior.

5.2. The Circadian Biological Clock

The daily rotation of the earth around its axis and its yearly rotation around the sun, impose on living organisms adaptation to diurnal and seasonal periodicity. In addition, the moon's monthly rotation around the earth (27.32 days orbital period or 29.53 days for an observer on Earth) seems to determine in a still unknown way the periodicity in human female fertility. Thus, all living organisms on Earth have adapted for millions of years to certain types of natural periodicity and have in this way become natural oscillators. This natural environmental periodicity has imposed on all living organisms a corresponding functional periodicity in accordance with its frequencies. In this way, all living organisms on Earth have developed endogenous molecular circadian and seasonal clocks to synchronize their behavioural, biological, and metabolic rhythms to natural environmental periodicity in order to perform at their best over a daily, monthly and yearly span.

This is a form of resonance between the periodicity of our environment seen as an "exciter" and living organisms seen as individual oscillators who perform at their maximum when the frequencies of the exciter coincide with their self-frequencies. Since all living organisms' "self-frequencies" are developed and stabilized by the periodicity of the natural environment during millions of years, if the periodicity of the environment changes artificially e.g. by exposure to light during normally dark periods of the 24-h cycle, the "exciter" changes its frequency and thus resonance is abolished.

In particular, the natural diurnal periodicity of light and dark is of apparent importance and the coordinated circadian regulation of sleep/wake, rest/activity, fasting/feeding, and catabolic/anabolic cycles is crucial for optimal health and well-being. Throughout the course of evolution, all animals and plants are exposed to regularly alternating periods of light and darkness during each day. This allowed species to adjust their physiology and synchronize it with the natural light/dark environment.

In order to achieve such a synchronization/resonance with the natural environment, vertebrates (including mammals) evolved a group of neurons to monitor the photoperiodic environment and to adjust accordingly the function of each single cell, organ, and their whole organism. It is a paired group of light-responsive neurons located in the mediobasal preoptic area at the diencephalic-telencephalic junction just anterior to the hypothalamus. Since these neurons lie immediately above the decussating axons of the optic nerve, *i.e.*, the optic chiasm, they are named the suprachiasmatic nuclei (SCN). The fact that the SCN in the anterior hypothalamus of the brain constitute the central biological clock in mammals has been known since 1972. The SCN consists of two regions of several clusters of small and densely packed paired neurons in which various peptidergic transmitters are expressed (Weaver 1998; Reiter et al 2011; Schwartz 2009).

The SCN clock is composed of multiple, single-cell circadian oscillators firing rhythmic nerve (electrical/chemical) impulses, which, when synchronized, generate co-ordinated circadian outputs that regulate the biological rhythms of the whole organism. The daily periodicity in the alternating intervals of light and darkness seems to be the most potent synchronizer for the SCN.

Light from the environment is perceived in the eyes by specialized intrinsically photosensitive retinal ganglion cells (ipRGC) containing the specialized photopigment, melanopsin, sensitive to blue wavelengths of about 460-480 μm (Kawasaki and Kardon 2007). The axons of these neurons travel in the optic nerve to the level of the optic chiasm where they then diverge to penetrate the SCN where they make synaptic contact with clock neurons. It is via this neural pathway, referred to as the retinohypothalamic tract, that the light/dark cycle adjusts continuously the function of the biological clock.

Thus, the SCN clock receives photic information via the retinohypothalamic tract. Retinal signals, mediated by glutamate, induce calcium release and activate a number of intracellular cascades involved in photic gating and phase shifting. Cell membrane events are directly involved in rhythmic expression. Calcium and potassium currents influence the electrical output of pacemaker neurons by altering shape and intervals of impulse prepotentials, afterhyperpolarization periods, and interspike intervals, as well as altering membrane potentials and thereby shaping the spontaneous rhythmic spiking patterns. As with the involvement of neuronal membrane events that play a crucial role, postsynaptic events and transmembrane ion fluxes are also essential elements in circadian rhythm generation and entrainment (Lundkvist and Block 2005).

The biological clock of the circadian timing system, composed of master molecular oscillators within the SCN, paces self-sustained and cell-autonomous molecular oscillators in peripheral tissues through electrical and chemical signals. In turn, circadian rhythms in gene expression synchronize biochemical processes and metabolic fluxes with the external environment, allowing the organism to function effectively in response to predictable physiological changes (Mazzoccoli et al 2012).

Each neuron in the SCN central clock has the necessary molecular machinery for generating circadian rhythmicity. The electric oscillations in the central clock neurons are electrically/chemically communicated to all molecular clocks in peripheral tissues cells. In this way the SCN regulate circadian rhythmicity in all peripheral tissues. In cases where the peripheral oscillators cease to be in tune with the central clock, circadian disruption (chronodisruption) results. To keep cellular rhythms in synchrony with the central clock, the system requires regular input from the ipRGC. We may speculate that the peripheral clocks in each individual cell of the organism are intimately related to the so called "spontaneous" intracellular ionic oscillations discovered in all types of cells (described in section 5.3 of the present chapter).

Clock oscillators have been found in many peripheral tissues, such as the liver, adipose tissue, intestine, heart and retina. All aspects of physiology and behaviour, including sleep/wake cycles, brain and cardiovascular activity, endocrine system, physiology of the gastrointestinal tract, hepatic metabolism, etc, are controlled by the circadian clock. The SCN clock not only sends signals to synchronize the molecular oscillators in peripheral tissues, but also to prevent the dampening of the circadian rhythms in these tissues. The SCN accomplish this task via neuronal connections or by triggering the circulation of humoral factors (Froy 2011).

The interplay between the central and the peripheral tissue clocks is not yet fully understood and remains a major challenge in determining how neurological and metabolic homeostasis is achieved across the sleep-wake cycle. Disturbances in the communication between the different individual body clocks can desynchronize the circadian system, which in turn may lead to unwell ness, chronic fatigue, decreased performance, obesity, neuropsychiatric disorders, and the development of different diseases (Albrecht 2012).

The hierarchical organization of the circadian system, through which the SCN central clock controls the peripheral circadian clocks in the cortex, the pineal gland, the liver, the kidney, the heart, and in every part of the body, ensures the proper timing of all physiological processes. In each SCN neuron, interconnected transcriptional and translational feedback loops enable the circadian expression of the clock genes. Although all the neurons have the same genotype, the oscillations of individual cells are highly heterogeneous in dispersed cell culture: many cells present damped oscillations and the period of the oscillations varies from cell to cell. These heterogeneous oscillations of individual cells are continuously adjusted and synchronized by the central SCN clock. In addition, the neurotransmitters that ensure the intercellular coupling, and thereby the synchronization of the cellular rhythms, differ between the two main regions of the SCN. Interestingly it seems that this cellular heterogeneity between the two regions is not detrimental to synchronization performances, but on the contrary helps resynchronization after jet lag. It seems that the heterogeneous architecture of the SCN decreases the sensitivity of the network to short entrainment perturbations while, at the same time, improving its adaptation abilities to long term changes (Hafner et al 2012).

Nutritional status is sensed by nuclear receptors and co-receptors, transcriptional regulatory proteins, and protein kinases, which synchronize metabolic gene expression and epigenetic modification, as well as energy production and expenditure, with behavioural and light-dark alternation. Physiological rhythmicity characterizes these biological processes and body functions, and multiple rhythms coexist presenting different phases, which may determine different ways of coordination among the circadian patterns, at both the cellular and whole-body levels. A complete loss of rhythmicity or a change of phase may alter the physiological array of rhythms, with the onset of chronodisruption or internal desynchronization, leading to metabolic derangement and disease, i.e., chronopathology (Mazzoccoli et al 2012).

The cycle of electrical activity of the SCN is not precisely 24 hours in duration, but it is, in fact, closer to 25 hours. Thus, the neural clock “runs slow”. Perhaps this is due to some form of natural dampening. If this rhythm would not be continuously adjusted closer to a 24-hour cycle, the physiology of the organism would run out of phase with the appropriate environmental time, in other words the organism would be desynchronized or chronodisrupted (Reiter et al 2011).

The SCN neuronal populations are mostly electrically silent during the night, start to fire action potentials near dawn and then continue to generate action potentials with a slow and steady pace all day long. Sets of currents of different ions like Na^+, K^+, and Ca^{2+} currents are responsible for keeping these daily rhythms. These rhythms in electrical activity which are crucial for the operation of the circadian timing system, including the expression of clock genes, are found to decline with ageing and disease (Colwell 2011).

One significant circadian element that transfers daily time information to the organism is the melatonin hormone cycle. Melatonin is mainly produced in the pineal gland (epiphysis) of the brain in mammals. It is a key hormone for the regulation of the whole body's biological cycle and has an oncostatic action preventing the development of different types of cancer. It is synthesized by the neurotransmitter serotonin which contains the amino acid tryptophan. Its concentration in the blood is always at low levels during the day and at high levels during darkness. Melatonin is also produced in the gastrointestinal tract by the entero-endocrine cells of the gut following ingestion of tryptophan-containing meal. The consequences of an altered melatonin cycle with chronodisruption have been linked to a variety of pathologies, including those of the gastrointestinal tract. When the photoperiodic environment is artificially perturbed, *e.g.*, with light exposure during the normal dark period, the central circadian pacemaker receives irregular information for that time, resulting in melatonin suppression and circadian disruption (Reiter et al 2011). We may also speculate that the same phenomenon may take place with exposure during the night to manmade radiation/EMFs. It is found that exposure to EMFs of different frequencies inhibits the synthesis of melatonin and reduces its oncostatic action (Cos et al 1991; Liburdy et al 1993).

SCN outputs control the daily rhythm in melatonin release from the pineal gland. In addition, many other hormones involved in metabolism, such as insulin, glucagon, adiponectin and corticosterone, exhibit circadian periodicity in their synthesis and action. Compelling evidence that the circadian clock controls metabolism and that circadian disruption is associated with multiple negative metabolic manifestations, is demonstrated by clock gene mutant mouse models. Thus, it seems that the synthesis of metabolic hormones is ultimately controlled by the SCN (Kalsbeek et al 2011; Froy 2011).

In the heart, ion channels on the plasma membrane of sinoatrial nodal pacemaker cells (SANCs) are the proximal cause of action potentials. Each individual channel type has been thoroughly characterized under voltage clamp recordings, and the ensemble of the ion channel currents generate rhythmic action potentials. Thus, this ensemble can be envisioned as a surface "membrane clock" (M clock). Localized subsarcolemmal Ca^{2+} releases are generated by the sarcoplasmic reticulum via ryanodine receptors during late diastolic depolarization and are referred to as an intracellular "Ca^{2+} clock," because their spontaneous occurrence is periodic during voltage clamp or in detergent-permeabilized SANCs. In spontaneously firing SANCs, the M and Ca^{2+} clocks do not operate independently but work together via numerous interactions modulated by membrane voltage, subsarcolemmal Ca^{2+}, protein kinase A, and calmodulin-dependent protein kinase II phosphorylation. Through these interactions, the two subsystem clocks become mutually entrained to form a robust, stable, coupled-clock system that drives normal cardiac pacemaker cell automaticity (Lakatta et al 2010). Finally, this coupled-clock system of the heart is controlled by nerve impulses from the SCN to be in tune with the central circadian biological clock. Thus, the rhythmic operation of the heart is also driven by the SCN.

Moreover, harmonic analysis of the alpha rhythm of brain bio-potentials has revealed that the brain contains several electromagnetic oscillators generating frequencies close to 10 Hz (Wiener 1963; Presman 1977). These brain oscillators probably result from combination of coherent ionic oscillations between a large number of brain cells which are also electrically/chemically tuned to the circadian clock.

The prominent influence of the circadian clock on human physiology is demonstrated by the temporal activity of a plethora of systems, such as sleep–wake cycles, feeding behaviour, metabolism, physiological and endocrine activity, and even the rhythmic function of the heart, the brain, and every single cell of a living body. Disrupted circadian rhythms will lead to attenuated feeding rhythms, unwell ness, disrupted metabolism, and eventually to disrupted health.

Probably it is not just the photic diurnal and annual periodicity that determine the function of the central biological clock (SCN) but also the diurnal and annual periodicity in the intensity of the terrestrial electric and magnetic fields. Yet such an influence is not investigated so far.

5.3. The Intracellular Electric Oscillations

In all kinds of cells investigated, spontaneous intracellular ionic oscillations in the ELF range (0.01-0.2 Hz) have been detected. These are rhythmic changes in the intracellular ionic concentrations, accompanied by corresponding oscillations in the plasma membrane potential. These harmonic oscillations of different types of free ions within cells like calcium (Ca^{2+}), potassium (K^{+}), sodium (Na^{+}), etc, and in particular calcium, seem to play a vital role in cellular and physiological functions as well as in embryonic development. Some of these oscillations result from periodic release of certain types of ions from intracellular reservoirs. In particular calcium oscillations seem to be initiated by periodic release of these ions by the endoplasmic reticulum (ER) (Berridge and Galione 1998).

These intracellular ionic oscillations are accompanied by oscillations in the potential difference across the membrane of the ER as well as the plasma membrane. It is not known whether membrane voltage oscillations precede ionic concentration oscillations or vice versa, but it seems to us that rather the opposite occurs: Ionic concentration oscillations are translated to electric charge fluctuations and this in turn is translated to voltage corresponding fluctuations between the external and the internal sides of a cell membrane. The intracellular ionic oscillations span the entire day and have been discovered in both animal and plant cells.

In particular, the fluctuations in the cytosolic concentration of free calcium ions seem to encode circadian clock signaling information as well as signaling information about diverse physiological and developmental events (Imaizumi et al 2007).

These periodical fluctuations in the concentration of free cytosolic calcium ion are found to promote cell phase transitions in early embryonic division and persist even if these transitions are blocked. These observations suggest that intracellular ionic oscillations and especially Ca^{2+} oscillations are essential timing elements of the early embryonic "master clock". This was observed in both sea urchin and Xenopus embryos (Craig et al 1997).

An ATP-dependent uptake of Ca^{2+} from the cytosol into the ER, the Ca^{2+} release from the ER through channels following a calcium-induced calcium release mechanism, and a potential-dependent Ca^{2+} leak flux out of the ER seem to occur. The binding of calcium to specific proteins such as calmodulin seems to be related to the fact that calcium oscillations in the cytoplasm can arise without a permanent influx of calcium into the cell (Marhl 1997).

Although the origin of the “spontaneous” ionic oscillations remains unknown, we may speculate that they are intimately connected with the circadian biological clock and thus possibly generated through a yet unknown way by rhythmic signals from the SCN, the periodicity of which is - as explained - imposed by the periodicity of our natural environment. They seem to constitute the peripheral clocks driven by the central (SCN) biological clock.

In addition, as we have suggested before (Panagopoulos et al 2000; 2002) the ELF frequencies of the intracellular ionic oscillations may represent the “self-frequencies” of individual cells and consequently of the whole living organism.

5.4. The Endogenous Electric Fields/Currents

It has been well documented that in all living organisms there are endogenous physiological, static electric fields within single cells or within whole tissues, with intensities 0.1-1 V/cm (10-100 V/m), controlling cell growth, division, differentiation, migration, wound healing, tissue regeneration after amputations or bone fractures, etc (McGaig and Zhao 1997; McGaig and Dover 1989; Nuccitelli 1988; 2000). These fields give rise to corresponding endogenous weak electric currents in certain directions, controlling cellular/tissue functions in these directions.

These endogenous electric currents consist of directed flows of certain types of ions through the plasma membrane and the cytoplasm of the corresponding cells. It was found that these endogenous electric currents are preceding cell growth and differentiation events and have always the same conventional direction with the growing part of the cell. These endogenous currents have been detected in all kinds of animal and plant cells studied so far in regard to these phenomena. These currents have a duration that usually ranges from a few hours to a few days (~ 10^4 - 10^6 sec) and display current densities between 1 and 100 μA/cm^2. No cellular or tissue growth has been observed so far without the existence of endogenous electric currents. Distortion, suppression, or nullification of these endogenous fields/currents with pharmacological agents or externally applied electric fields of opposite polarity, results in distortion or cessation of the corresponding cellular/tissue function (development, proliferation, differentiation, wound healing, regeneration, etc), while enhancement with externally applied fields of similar polarity increases the rate of this function (Weisenseel 1983; Lee et al 1993; Nuccitelli 2000).

Moreover, in all animals there is a potential difference across the epithelium called the trans-epithelial potential (TEP). TEP in the intact epithelium around a wound acts like a battery, giving rise to significant ion flux and electric current at the wound. These circulating endogenous currents generate an electric field oriented towards the wound, with the wound as the cathode (Reid et al 2011).

Similar endogenous electric currents control not only cell growth, proliferation, differentiation, and wound healing but all other cellular functions as well, such as signal transduction, synthesis and release of enzymes, etc (Lee et al 1993; Messerli and Graham 2011).

Physiological direct current (DC) electric fields with intensities 10-100 V/m have been measured in developing chicken and amphibian embryos as well as in adult tissues near skin wounds. This is in agreement with the above observations that endogenous electric fields play a crucial role in development, regeneration and wound healing. Endogenous fields of 20-30 V/m have been measured just beneath the epidermis of chick and frog embryos and the distortion of these physiological fields results in abnormal development. Endogenous electric fields of 60-100 V/m have been measured in regenerating epidermal wounds in all animals and in regenerating amphibian limbs (Nuccitelli 2000).

Electric fields are applied clinically to humans in order to provide stronger signal for the enhancement of healing of chronic wounds. Although clinical trials during the last decades have shown that applied electric fields enhance healing of chronic wounds, the mechanisms by which cells sense and respond to external EMFs remain under investigation.

Nevertheless, it is understood that plasma membrane voltage-gated ion channels play a major role, and that the cell membrane is the site of perception and transduction of information that generates the endogenous electric currents (Messerli and Graham 2011). An early hypothesis made by Jaffe (1979) assumes that the triggering of exogenous or endogenous factor(s) to initiate spatial growth and differentiation of a cell is perceived asymmetrically around the cell by specific receptors on the plasma membrane, causing a slight and transient asymmetry in the arrangement of ion pumps and channels on its surface. This in turn generates an electric current consisting of mobile ions entering the cell at one site and pumped out at another. [In section 6.2 of the present chapter we describe a mechanism by which weak externally applied electric or magnetic fields may affect cell function by changing intracellular ionic concentrations through irregular gating of voltage-gated channels on cell membranes (Panagopoulos et al 2000; 2002)].

Externally applied static electric fields of similar intensities with the endogenous fields are found to direct cell migration, cell proliferation, stimulate mammalian and amphibian nerve regeneration, and nerve sprouting at wounds, wound healing, or spinal cord injury healing (Borgens 1988; Borgens et al 1986a; 1986b; Wang and Zhao 2010). Accordingly, pulsed ELF magnetic fields (having the ability to induce corresponding electric ones) are found to accelerate bone regeneration and bone fracture healing in mammals (Brighton et al 1979; 1989; Brighton and McClusky 1987; Brighton and Townsend 1988; Bassett et al 1964).

In the alga *Vaucheria*, visible electromagnetic radiation (blue light) induces changes in the plasma membrane that cause ionic currents to pass through the membrane. The zygotes of brown algae *Fucus* and *Pelvetia*, when illuminated by linearly polarized light, germinate parallel to the electric vector. The same brown algae are found to germinate toward the side of the zygote with higher K^+, Ca^+, or H^+ concentrations. An electric current with density 1-2 $\mu A/cm^{-2}$ starts to enter the shaded side of unilateral irradiated cells, about 2-3 h after fertilization. It is also found that pollen grains of *Lilium* and spores of *Equisetum* germinate toward the positive electrode in a DC externally applied electric field or parallel to an externally applied strong magnetic field (Weisenseel 1983).

Such orientation effects induced by external EMFs may be controlled by endogenous electric currents after depolarization of the cell membrane or alterations in intracellular ionic concentrations, especially Ca^{2+}. Irradiation with red light causes a Ca^{2+} -dependent depolarization of the cell membrane by about 60 mV in the green alga *Nitella*, and increased uptake of Ca^{2+} in the cells of the filamentous alga *Mougeotia*. Activation of fish eggs or sea urchin eggs by the entry of sperm, induces a large increase in cytosolic free Ca^{2+} concentration as well as an elevation in the internal pH-value (Weisenseel 1983).

In a recent study, it was shown that directed neuronal migration depends on the establishment of cell polarity, and cells are polarized dynamically in response to extracellular electromagnetic signals. In particular, it was shown that cell division of cultured hippocampal cells is oriented by an applied electric field, which also directs neuronal migration. Directed migration involved polarization of the leading neurite, of the microtubule-associated protein MAP-2, the Golgi apparatus, and the centrosome, all of which repositioned asymmetrically to face the cathode of the applied field (Yao et al 2009).

Thus, it seems that externally applied electric fields of similar (or even smaller) intensity and similar polarity with the corresponding physiological endogenous ones can be used as a novel type of therapy regarding tissue repair and regeneration. Combination of the electric stimulation and other well understood biochemical regulatory mechanisms may offer powerful and effective therapies for tissue repair and regeneration (Wang and Zhao 2010).

Cells are found to respond *in vitro* to external DC electric fields (aligning, migrating, or growing along a direction with respect to the applied electric field), at a threshold between 3 and 7 V/m (Nishimura et al 1996; Huang et al 2009; McKasson et al 2008; Messerli and Graham 2011). Moreover, soft tissue preparations like bovine fibroblasts, chicken tendons, etc, are found to respond to externally applied electric fields (by changes in protein synthesis, proliferation, alignment with respect to the field direction, etc), at very low thresholds ~ 4 mV/m (McLeod et al 1987; Cleary et al 1988; Lee et al 1993). These intensities are significantly smaller that those of endogenous physiological electric fields described in the previous paragraphs.

Since cells are found to respond to external EMFs at intensities of the order of $\sim 10^{-3}$ V/m, it follows that externally applied EMFs of much larger intensities like those accounted in modern human residential and working environment may interact (directly or indirectly) with the endogenous physiological fields. Such an interaction would cause an alteration in the parameters of these fields (intensity, direction, etc) and a consequent alteration in their corresponding functions. Perhaps this should be the focus for the explanation of the biological action of natural and man-made environmental EMFs. In the following paragraphs we shall describe two plausible ways for this interaction.

6. Distortion of Endogenous Electric Fields by External EMFs

6.1. Distortion of Endogenous Electric Fields by Direct Electromagnetic Interference with External Fields

An intracellular (endogeneous) electric field originating from ion concentration difference across two different cell sites and controlling specific cellular/physiological functions, will interact with any external electric field by simple vector addition giving a resultant field which will be of different magnitude, frequency, and direction than the original intracellular field. Apart from the interaction with the endogenous fields, the external field will cause a polarization of the biological tissue containing the specific cell(s). More specifically:

Polarization of Biological Tissue: Any externally applied electric field $\vec{E}_{ex}$ will, theoretically, induce a polarization of biological matter by rearranging the electric charges in the extracellular aqueous solution and even on the cell membrane and the intracellular solutions as well. This re-localization of electric charge will be most evident in the "free" (mobile) ions which are loosely bound to water molecules and carry a net electric charge. In other words, the induced polarization will - theoretically - alter free ion distribution and bind a number of charge carriers (free ions) to certain positions, decreasing their mobility and their availability to be used for keeping the correct ionic concentrations and the cells' electrochemical equilibrium. This condition represents anyway a stress for the organism. The cells will then be forced to keep their electrochemical balance (correct ionic concentrations in every site of the cytoplasm and of the external surface of the cell membrane) by active ion transport (i.e. by activating pumps like for example the K^+-Na^+ ATPase, or other protein pumps). Activation of pumps will in turn increase the energy consumption by the cells by decreasing ATP which is the main energy storage molecule. In other words, the organism overcomes the stress by energy consumption.

The induced polarization/rearrangement of electric charges within the biological tissue generates a polarization field $\vec{E}_p$ in opposite direction of the externally applied field $\vec{E}_{ex}$. The intensity of the polarization field varies in different sites of the biological tissue and between different sites of each cell depending on local permittivity and charge availability. The magnitude of the polarization field is given by application of Eq (1) (Gauss law for the electric field) within the tissue:

$$E_p = \frac{1}{\varepsilon\varepsilon_o} \cdot \frac{q_p}{S} \tag{35}$$

where q_p is the polarization charge, ε the local tissue permittivity, and S a surface area vertical to the polarization field containing the charge q_p.

The polarization field will never be larger in magnitude than the external field: $E_p \leq E_{ex}$. [In metals $E_p \cong E_{ex}$, resulting to nullification of the field within their interior. In biological tissue the polarization field is in any case smaller than the external field: $E_p < E_{ex}$].

The remaining - resultant field induced within e.g. a cell by the externally applied field, will be called internal or induced electric field $\vec{E}_{in}$ and it will be the difference between the external field and the polarization field:

$$\vec{E}_{in} = \vec{E}_{ex} - \vec{E}_p \tag{36}$$

For example, in case that the external field is of a sinusoidal alternating magnitude (as those associated with power lines) with a circular frequency ω, $E_{ex}=E_o sin\omega t$, then from Eqs. (35), (36), the vector of the internally induced electric field each moment is given by:

$$\vec{E}_{in} = (E_o\, sin\omega\, t - \frac{1}{\varepsilon\varepsilon_o} \cdot \frac{q_p}{S})\ \vec{u}_{ex} \tag{37}$$

(where $\vec{u}_{ex}$ is the unit vector parallel to the external field $\vec{E}_{ex}$).

Although these equations show that there is always a change in the magnitude of the externally applied field within the tissue due to polarization, the calculation of the polarization field is not an easy task, mainly due to the difficulty in the calculation of the polarization charge. Since according to experimental evidence (section 5.4), cellular processes associated with specific endogenous fields are found to be altered (enhanced, diminished and even nullified) by externally applied fields of similar or even significantly smaller intensities than the endogenous ones (Borgens 1988; Borgens et al 1986a; 1986b; Brighton et al 1979; 1989; Brighton and McClusky 1987; Brighton and Townsend 1988; Bassett et al 1964; Lee et al 1993; Wang and Zhao 2010; Messerli and Graham 2011), it comes that the polarization of biological tissue induced by external fields must either be very small and it does not reduce significantly the external fields (as would happen e.g. with a Faraday cage where the polarization field is equal and opposite to the external field and thus the field is zero within a metal conductor placed within an external field as mentioned already), or the external electric fields interact by indirect ways with the endogenous ones (as described in section 6.2). In any case, biological matter is not metal to shield the externally applied fields as supported by others (Adair 1991b). Instead of the free electrons in metals, biological tissue's carriers are mainly the mobile ions (transiently bound to water molecules) the mobility of which is much less than that of free electrons.

Interaction with Endogenous Fields: The remaining/resultant internally induced electric field $\vec{E}_{in}$ whatever it is, will be in the same direction as the external field and it will interact directly with any endogenous physiological electric field $\vec{E}_{end}$ by simple vector addition, resulting in distortion of the endogenous physiological field to some degree significant or insignificant depending on polarization as explained. The distorted endogenous field, which we shall name $\vec{E}'_{end}$, will be the sum vector of the physiological endogenous field plus the internally induced field:

$$\vec{E}'_{end} = \vec{E}_{end} + \vec{E}_{in} \tag{38}$$

This final/distorted endogenous field will have a significantly or insignificantly altered magnitude, direction and even frequency than the original physiological endogenous field.

In the case of an alternating external field, according to Eqs (37), (38) the vector of the final distorted endogenous field will theoretically be given by:

$$\vec{E}'_{end} = \vec{E}_{end} + (E_o \sin\omega t - \frac{1}{\varepsilon\varepsilon_o} \cdot \frac{q_p}{S})\, \vec{u}_{ex} \tag{39}$$

Any distortion of the physiological endogenous field, if not properly corrected by cell's homeostasis (e.g. by enforcing the original endogenous field by active ion transport/pump activation and consequent ATP consumption), will result in a corresponding distortion of the cellular/physiological functions controlled by the original physiological endogenous field.

Even if the polarization field is large enough to significantly attenuate the induced field within the biological tissue, the polarization itself represents an altered condition for the living organism (as already explained), decreasing the availability of carriers (mobile ions) to participate in the physiological endogenous functions, and this will also require ATP consumption in order to be corrected e.g. by active ion transport.

Thus, eventually, the interaction of external EMFs with biological tissue will result in either energy (ATP) consumption, or distortion of cellular/physiological functions, or both. Thus, even if the external field will not cause alteration in physiological functions, it will cause additional energy consumption by the organism.

Again, we should emphasize that, since cellular/physiological functions controlled by endogenous fields are found to be nullified by application of external fields of similar intensities and polarities opposite to the endogenous ones, the polarization field must either be of very small importance, or the external fields interact with the endogenous ones in indirect ways as shown below. We consider that this second option might be more probable.

6.2. Distortion of Endogenous Electric Fields by Alteration of Intracellular Ionic Concentrations

Endogenous electric fields originate from ionic concentration differences between different sites of the cytoplasm. The resulting endogenous currents are positive ion flows towards lower electrical potential and/or negative ion flows towards higher potentials. It is therefore obvious that alteration of intracellular ionic concentrations by any external factor (e.g. an external EMF), if not corrected by cell's homeostasis e.g. by active ion transport and consequent ATP consumption as already mentioned, may result in distortion of physiological intracellular electric fields and currents.

It has been shown that intracellular ionic concentrations may be altered by interaction of external oscillating EMFs with voltage-gated channels on cell membranes and irregular gating of these channels, according to the Ion Forced-Vibration Theory that we have proposed (Panagopoulos et al 2000; 2002). This irregular gating of ion channels may lead, nonthermally, to disruption of the cell's electrochemical balance and function, as we describe below.

According to this theory which is considered so far the most valid one of all the proposed theories, (Creasey and Goldberg, 2001; Halgamuge and Abeyrathne 2011), even very weak ELF electric fields on the order of 10^{-4} V/m, are theoretically able to change the intracellular ionic concentrations and thus, disrupt cell function. Since all types of RF-microwave radiation and especially those used in modern mobile telecommunications are always transmitted in ELF pulses, or include ELF modulating signals of intensities usually thousands of times higher than 10^{-4} V/m, this theory can be applied for the explanation of their bioeffects.

The basic idea is based on the fact that any external oscillating electric or magnetic field, induces a forced-vibration on the mobile ions inside and outside of all living cells in the exposed biological tissue. When the amplitude of this forced-oscillation exceeds some critical value, the electrostatic force exerted by the oscillating ions' charge on the electric sensors of the voltage-gated membrane ion channels, can irregularly gate these channels, resulting in alteration of the intracellular ionic concentrations.

As already explained, mobile ions play a key role in all cellular functions, and alterations in their intracellular concentrations initiate or accompany all cellular biochemical/biophysical processes.

Consider an external oscillating electric field (or the electric component of an electromagnetic wave) inducing an internal field of intensity E within the biological tissue, and acting in the $\vec{x}$ direction on a free ion in the vicinity of a cell membrane.

The forced-oscillation of each free ion due to the external oscillating field is described by the equation:

$$m_i \frac{d^2x}{dt^2} + \lambda \frac{dx}{dt} + m_i \omega_o^2 x = E_o z q_e \sin\omega t \tag{40}$$

in the case of an external harmonically oscillating electric field, inducing a corresponding internal field $E = E_o \sin\omega t$, with circular frequency $\omega = 2\pi\nu$, (ν, the frequency in Hz), where: z is the ion's valence, $q_e = 1.6\times10^{-19}$ C the elementary charge, $F_1 = E_o z q_e \sin\omega t$ is the force exerted on the ion by the field, $F_2 = -m_i \omega_o^2 x$ is a restoration force proportional to the displacement x of the free ion, m_i the ion's mass and $\omega_o = 2\pi\nu_o$, with ν_o the ion's oscillation self-frequency if the ion was left free after its displacement x. In our case, this restoration force is found to be very small compared to the other forces and thus it does not play an important role. $F_3 = -\lambda u$ is a damping force, where $u = \frac{dx}{dt}$ is the ion's velocity due to the forced-oscillation and λ is the attenuation coefficient for the ion's oscillation, which for the cytoplasm or the extracellular medium is calculated to be $\lambda \cong 10^{-12}$ Kg/sec, while for ions moving inside channel proteins, is calculated to have a value: $\lambda \cong 6.4\times10^{-12}$ Kg/sec, (in the case of Na^+ ions, moving through open Na^+ channels) (Panagopoulos et al 2000).

Assuming that the ions' self-frequencies coincide with the frequencies of the cytosolic free ions' spontaneous oscillations (described in section 5.3) observed as membrane potential spontaneous oscillations in many different types of cells with values smaller than 1 Hz and assuming that the ion's maximum oscillation velocity has a value of 0.25 m/s, as calculated for the movement of sodium ions through open sodium channels using patch-clamp conductivity data (Panagopoulos et al 2000), it comes after operations that the general solution of equation (40), is:

$$x = \frac{E_o z q_e}{\lambda\omega} \cos \omega t - \frac{E_o z q_e}{\lambda\omega} \tag{41}$$

Since the second term of the second part of equation (41) is constant, the oscillating movement is described by the first term:

$$x = \frac{E_o z q_e}{\lambda\omega} \cos \omega t \tag{42}$$

Eq. (42) shows that the free ion's forced-oscillation is in phase with the external force. The amplitude of the forced-oscillation is:

$$A = \frac{E_o z q_e}{\lambda\omega} \tag{43}$$

Thus, the amplitude is proportional to the intensity and inversely proportional to the frequency of the oscillating field.

Equation (41) declares that, at the moment when the external field is applied and at the moment when it is interrupted, the displacement of the ion becomes twice the amplitude of the forced vibration, because of the constant term which adds to the amplitude. For pulsed EMFs, this takes place continuously with every repeated pulse. This explains why pulsed EMFs are reported to be more bioactive than continuous ones of the same other characteristics (Goodman et al 1995).

The coherently oscillating ions due to the action of the external EMF represent a periodical displacement of electric charge, able to exert coherent forces on every fixed charge of the membrane, such as the charges on the voltage sensors of voltage-gated ion channels.

Once the amplitude of the ion's forced-oscillation exceeds some critical value, the coherent forces that the ions exert on the voltage sensors of the voltage-gated membrane channels can trigger the irregular opening or closing of these channels, disrupting in this way the cell's electrochemical balance and function, by altering the intracellular ionic concentrations.

Voltage-gated channels are leak cation channels. The state of these channels, (open/closed), is determined by electrostatic interaction between the transmembrane voltage and the channels' voltage sensors. They interconvert between open and closed state, when the electrostatic force, exerted by transmembrane voltage changes on the electric charges of their voltage sensors, transcends some critical value.

The voltage sensors of these channels, as already mentioned, are four symmetrically arranged, transmembrane, positively charged a-helices, each one designated S4, (Noda et al 1986; Stuhmer et al 1989).

It is known that changes of about 30 mV in the transmembrane voltage, are able to gate these electrosensitive channels by exerting the necessary electrostatic force on the fixed charges of the S4 helices (Bezanilla et al 1982; Liman et al 1991; Lecar et al 2003).

It has been shown that a single ion's displacement ∂r, of $\sim 10^{-12}$ m, in the vicinity of S4, can exert an electrostatic force on each S4, equal to that exerted by a change of 30 mV, in the transmembrane voltage, (Balcavage et al 1996; Panagopoulos et al 2000):

The intensity of the transmembrane electric field is:

$$E_m = \frac{\Delta\Psi}{s} \tag{44}$$

where, $\Delta\Psi$ is the transmembrane voltage and s the membrane's width.

In addition, $E_m = \dfrac{F}{q}$ (45)

where F in this case is the force acting on an S4 domain and q is the effective charge on each S4, which is estimated to have a value (Liman et al 1991):

$$q \cong 1.7\ q_e \tag{46}$$

From equations (44), (45) we obtain:

$$F = \frac{\Delta\Psi}{s}\, q \ \Rightarrow \partial F = \partial\Delta\Psi\ \frac{q}{s} \tag{47}$$

(where $\partial\Delta\Psi$ is the change in the transmembrane voltage, necessary to gate the channel). For $\partial\Delta\Psi$=30 mV, s=10^{-8}m and substituting q from (46), equation (47) gives: $\partial F = 8.16 \times 10^{-13}$ N.

This is the force, on the voltage sensor of a voltage-gated channel, required normally, to interconvert the channel between closed and open state.

The force acting on the effective charge of an S4 domain, via an oscillating, free z-valence cation, is: $F = \dfrac{1}{4\pi\varepsilon\varepsilon_o} \cdot \dfrac{q \cdot zq_e}{r^2} \Rightarrow$

$\partial F = \text{-}2 \cdot \dfrac{1}{4\pi\varepsilon\varepsilon_o} \cdot \dfrac{q \cdot zq_e}{r^3}\ \partial r \Rightarrow$ (ignoring the minus sign),

$$\partial r = \frac{2\pi\varepsilon\varepsilon_o \partial F \cdot r^3}{q \cdot zq_e} \tag{48}$$

This is the minimum displacement of a single, z-valence cation, in the vicinity of S4, able to generate the necessary force ∂F to gate the channel. Where: r is the distance between the free ion with charge zq_e and the effective charge q on each S4 domain, which can be conservatively taken as 1 nm (Panagopoulos et al 2000), since the concentration of free ions on both sides of mammalian cell membranes, is about 1 ion per nm^3 (Alberts et al 1994). The relative dielectric constant ε can have a value 80 for a water-like medium, (cytoplasm or extracellular space), or a value as low as 4 for channel-proteins, (Honig et al 1986; Leuchag 1994).

Let us calculate ∂r for one single-valence cation, interacting with an S4 domain. If two or more single-valence cations interact (in phase) with an S4 domain from 1nm distance, ∂r

decreases proportionally. For ions moving inside channel-proteins, we assume that they move in single file (Palmer 1986; Panagopoulos et al 2000).

From equation (48) and for $\partial F = 8.16 \times 10^{-13}$ N, we get:

$\partial r \cong 0.8 \times 10^{-10}$ m, (for ε = 80)

and: $\partial r \cong 4 \times 10^{-12}$ m, (for ε = 4) (49)

Thus, only one single-valence cation's displacement of only a few picometers from its initial position, is able to interconvert voltage-gated channels, between open and closed states, (for cations moving or bound within channels).

Therefore, any external field, which can induce a forced-oscillation on mobile ions, with an amplitude $A \geq 4 \times 10^{-12}$ m, is able to irregularly gate electrosensitive channels and disrupt the cell's function. Substituting A from Eq. (43) in the last condition, it comes that, a bioactive external oscillating electric field of internal intensity amplitude E_o and circular frequency ω inducing a forced-oscillation on every single-valence ion (z=1), satisfies the condition:

$$\frac{E_o q_e}{\lambda \omega} \geq 4 \times 10^{-12} \text{ m} \quad (50)$$

Since we adopted a value for ∂r ($\cong 4 \times 10^{-12}$ m) valid for cations within channels (where $\varepsilon = 4$), we shall use the corresponding value for λ, calculated also for cations moving within channels (Panagopoulos et al 2000): $\lambda \cong 6.4 \times 10^{-12}$ Kg/s.

Thereby, the last condition becomes:

$$E_o \geq \omega \times 1.6 \times 10^{-4} \quad (51)$$

or $$E_o \geq \nu \times 10^{-3} \quad (52)$$

(ν in Hz, E_o in V/m)

If two or more cations interact (in phase) with an S4 domain from 1nm distance, ∂r in (49) decreases proportionally. The concentration of free ions on both sides of mammalian cell membranes is about 1 ion per nm^3, as mentioned, and for this we have initially calculated ∂r for one cation interacting with an S4 domain, although it is very likely that several ions interact simultaneously each moment with an S4 domain from a distance of about 1nm. This applies also for ions moving already within channels, since it is known that although they pass through the narrowest part of the channel in single file (Miller 2000; Palmer 1986; Panagopoulos et al. 2002), several ions fill the pore each moment as they pass sequentially and several ion-binding sites (three in potassium channels) lie in single file through the pore, close enough that the ions electrostatically repel each other (Miller 2000).

Thus, if two single-valence (z =1) cations interact with the channel's sensor, the first part of cond. (50) is multiplied by 2. Moreover, if they are double valence cations (z =2), the first part is multiplied by 4 while at the same time the second part is divided by 2, according to Eq. (48). Moreover, for pulsed fields, the first part is again multiplied by 2 as explained.

Therefore, in the case of pulsed fields and for only two double-valence cations (i.e. Ca^{+2}) interacting simultaneously with the S4 channel sensor, the first part of the cond. (50) is multiplied by 8 and the second part divided by 2. Thus finally, the second part is divided by 16 and the condition for irregular gating of the channel becomes:

$$E_o \geq \nu \times 0.625 \times 10^{-4} \tag{53}$$

(ν in Hz, E_o in V/m).

Whenever condition (53) is satisfied for the induced internal field amplitude E_o, the external field can irregularly gate the ion channel.

Condition (53) declares that ELF electric fields with induced internal intensities even smaller than 0.1 mV/m (= 10^{-4} V/m) are theoretically able to disrupt cell function by irregular gating of ion channels.

In the cases of cells of surface tissues, like skin cells, nerve cells reaching the skin, eyes, etc, condition (53) is also satisfied for the intensity of the external field. For inner cells and tissues, the externally applied field will - theoretically - be diminished to a varying degree, due to polarization (as explained in section 6.1). Since external electric fields are found to have a biological action at thresholds ~10^{-3} V/m, it follows that any polarization effects do not reduce significantly the action of external electric fields as probably takes place due to the described mechanism.

Respectively, an externally applied alternating magnetic field $B=B_o sin\omega t$ will also induce a forced oscillation on the mobile ions. The ion displacement due to the magnetic field after substituting the electric force by a corresponding magnetic one

$$F'_1 = B_o u\, z\, q_e \sin\omega t \tag{54}$$

will be described by an equation similar to Eq (40):

$$m_i \frac{d^2x}{dt^2} + \lambda \frac{dx}{dt} + m_i\, \omega_o^2 x = B_o u\, z\, q_e \sin\omega t \tag{55}$$

The ion's maximum displacement, (amplitude of the corresponding forced-oscillation) due to a magnetic field as described by Eq (55), is calculated to be normally much smaller than the corresponding displacement due to an electric field of the same frequency (given by Eq 43).

The corresponding bioactivity condition to (53) for the magnetic field B in G (which is the unit for environmentally encountered magnetic field intensities) is:

$$B_o \geq 2.5\,\nu \tag{56}$$

(ν in Hz, B_o in G)

Comparing the conditions (53) and (56) for the biological activity of oscillating electric and magnetic fields respectively, it looks as magnetic fields are less bioactive than electric ones of the same frequency. Nevertheless, a large number of experimental and epidemiological data suggest intense biological activity of manmade ELF magnetic fields (Goodman et al 1995; Wertheimer and Leeper 1979; Savitz et al 1988; Feychting and Ahlbom 1993; 1994; 1995; Coleman et al 1989; Draper et al 2005). A possible explanation is that the magnetically induced electric field is rather the bioactive component than the magnetic field itself. This conclusion arising from our presented theory is in agreement with several experimental/epidemiological observations indicating that the magnetically induced electric field is probably the actual bioactive component instead of the magnetic field itself (Koana et al 2001; Liburdy 1992; Greene et al 1991; Coghill et al 1996).

It is important to note that the magnetically induced electric field given by Maxwell's third equation (3), is always naturally produced and co-existing with any time-varying magnetic field and, especially in the case of ELF fields, there is no way to totally eliminate it or insulate it by shielding. [Metal grids can reduce ELF electric fields to a certain degree but not totally eliminate them. For a significant decrease, a closed metal box is necessary].

The magnetically induced electric field has the same waveform and the same frequency as the magnetic one that generates it. The two fields have a phase difference of $\pi/2$ between them. Thus, in reality there is never any pure exposure to a time-varying magnetic field without a simultaneous exposure to a corresponding induced electric one.

The reverse does not occur: In the case of a time-varying electric field, the corresponding induced magnetic one, given by the second term of the second part of Maxwell's fourth equation (4), is usually of negligible intensity due to the small value of the constant product $\varepsilon_o \mu_o$ included in this term.

For any biological effect produced by a combination of the two co-existing fields (in case of time-varying magnetic field exposures), it is unknown whether it is due to the magnetic or to the corresponding induced electric field or due to the combination of both. Yet, the majority of the studies seem to ignore the induced electric field and concentrate only on the magnetic component.

According to the described mechanism, lower frequency fields are more bioactive than higher frequency ones as indicated by Eq (43). Thereby, ELF fields are especially bioactive according to this mechanism. This applies not only to purely ELF fields as those associated with electric power production (50-60 Hz), but also to the ELF pulses or modulation signals associated with microwave radiation. Microwave radiation is always pulsed or modulated by ELF frequencies in order to be able to carry and transmit information as already stated.

In addition, pulsed fields are shown to be more bioactive than continuous (uninterrupted) ones because of the constant term in the second part of Eq. (41) which doubles the displacement of the oscillating ions at the onset and at the end of every pulse (Panagopoulos et al., 2002).

The ELF pulses of the mobile telephony signals as well as of any other type of modern microwave radiation are certainly of adequate intensity to produce biological/health effects on living organisms according to this mechanism.

The threshold ELF intensities predicted by the present mechanism to be able to alter biological function ($\sim 10^{-4}$ V/m), being in agreement with the experimentally observed thresholds ($\sim 10^{-3}$ V/m) (section 5.4), are millions of times smaller than the current ELF exposure limits ($\sim 10^{4}$ V/m) (ICNIRP 1998).

6.3. EMF-Induced Displacement of Mobile Ions Cannot Be Masked by Thermal Motion

Certainly, free ions move anyway because of thermal activity, with kinetic energies much larger normally (millions of times as already shown), than the ones acquired due to the action of an external electromagnetic field at intensities encountered in the human environment. For this, it has been claimed (Adair 1991a) that thermal motion masks the motion induced by the external field, making this motion unable to produce any biological effect.

But as we have explained (Panagopoulos et al 2000; 2002), thermal motion is a random motion, in every possible direction, different for every single ion, causing no displacement of the ionic "cloud" and for this it does not play any particular role in the gating of channels, or in the passing of the ions through them. On the contrary, forced-vibration is a coherent (in phase) motion of billions of ions together in the same direction. The thermal motion of each ion and moreover the thermal motion of many different ions, results in mutually extinguishing forces on the voltage sensor of an electrosensitive ion channel, while the coherent - parallel motion of the forced-oscillation results in additive forces on the voltage sensor.

Even if we consider only one single-valence ion interacting with an S4 domain, this ion moving with a drift velocity u = 0.25 m/s due to the forced-oscillation, it needs a time interval $\partial t = \frac{\partial r}{u} \cong 1.6\times10^{-11}$ s, in order to be displaced at the necessary distance $\partial r = 4\times10^{-12}$ m [according to Eq (49)].

The ions' mean free path in the aqueous solutions around the membrane is about 10^{-10} m, (Chianbrera et al. 1994), and it is certainly smaller within the channels, (the diameter of a potassium ion is about 2.66×10^{-10} m and the diameter of the narrowest part of a potassium channel is about 3×10^{-10} m, thereby the mean free path of a potassium ion within the channel has to be on the order of 10^{-11} m), (Panagopoulos et al. 2002; Miller 2000).

During the same time interval ∂t, this ion will also be displaced by its thermal motion, at a total distance $\partial r_{kT} = u_{kT} \cdot \partial t$ which, according to Eq (32) gives:

$$\partial r_{kT} = \sqrt{\frac{3kT}{m_i}}\,\partial t \quad \cong 930 \times 10^{-11}\,\text{m}$$

Therefore the ion within the above time interval δt, will run because of its thermal activity, ~930 (in other words hundreds/thousands) mean free paths, each one in a different direction, exerting mutually extinguishing opposing forces on the channel's sensors, while at the same time the ion's displacement because of the external field is in a certain direction, exerting on each S4 domain a force of constant direction.

If in addition we consider several ions interacting simultaneously with the S4 domain, then the effect of the external field is multiplied by the number of ions, whereas the effect of their random thermal motions becomes even more negligible.

Thus thermal motion, although normally thousands of times larger (corresponding to millions of times larger kinetic energies), is unlikely to mask the displacement of the mobile ions caused by external EMFs, according to this analysis.

7. ENDOGENOUS ELECTRICAL BALANCE IN LIVING ORGANISMS DETERMINES HEALTH AND WELL-BEING

The presented data in section 5 of this chapter show the electric nature of all living organisms. The endogenous electric currents, the intracellular electric oscillations, the cell membrane electrical potential, and the function of the circadian biological clock are characteristic manifestations of this subtle and unique electric nature. The oscillating (time-varying) kind of this electric nature makes it electromagnetic. The present study is probably the first attempt to present these individually observed bio-electromagnetic manifestations in living organisms as mutually connected. The described electromagnetic nature of living organisms is supposed to be in tune (resonance/harmony) with the electromagnetic natural environment.

It is clear that weak endogenous periodically varying physiological electric fields in living organisms play a fundamental role in all their physiological functions. Since distortion in the physical parameters of these fields results to the cessation or alteration of the corresponding biological/physiological functions, it comes that these endogenous physiological fields should not be distorted by external fields. Moreover, since endogenous physiological fields can be altered by external ones of significantly smaller intensities according to both experimental and theoretical evidence, it follows that the electrical balance of living organisms is a very delicate one, and can be very easily disrupted by external EMFs. In other words, endogenous electrical balance in living organisms cannot occur in the presence of unnatural – manmade – electromagnetic pollution in the environment. Since this pollution is inevitably connected with human technological evolution, we must find the maximum exposure levels from artificial EMFs that can be tolerated by living organisms without adverse health consequences.

These actual maximum permissible exposure levels that would be tolerated by the living organisms and would not disturb their physiological function, seem to be thousands of times below the current exposure limits according to both experimental/epidemiological evidence and theoretical calculations. For example, GSM mobile phone radiation is found to cause DNA damage on insect reproductive cells (gametes) and adversely affect reproduction for intensities down to 1 $\mu W/cm^2$ after only a few minutes daily exposure (Panagopoulos et al 2010). This intensity value is between 450 and 950 times smaller than the corresponding limits for 900 and 1900 MHz microwave radiation emitted by these devices (ICNIRP 1998). Moreover, the presented mechanism in section 6.2 shows that ELF electric fields of only $\sim 10^{-4}$ V/m intensity can disrupt physiological cell function. This intensity is about 10^8 times (a hundred million times) lower than the 50-60 Hz current electric field exposure limit (5-10 kV/m) (ICNIRP 1998).

According to Liboff (2009), wellness can be described in physical terms as a state that is a function of the organism's electric polarization by environmental EMFs. Any application of manmade EMFs is combined in any case with the continuous exposure to the natural (terrestrial) fields. Living organisms have adapted throughout evolution to the subtle polarization caused by the “steady” natural fields. One can alter tissue polarization by application of external EMFs in different combinations with the natural ones. Even when exposure to manmade EMFs does not result to an alteration of the endogenous physiological fields, the additional polarization that generates within the biological tissue represents a stress for the organism as explained. A healthy organism overcomes the additional stress by additional energy (ATP) consumption, but it might not be the same for young organisms during development, old organisms, or even healthy organisms during combined stress (co-stress) conditions, during sickness, etc. The strikingly low EMF intensities which are found to alter biological function (described in section 5.4) is a fact intimately connected with the existence of physically equivalent endogenous weak electric fields as explained in the present study. These very low intensities found experimentally to affect biological function are in agreement with the intensities predicted by at least one of the mechanisms presented in the present study (section 6.2). These facts make claims related to electromagnetic pollution more credible and also provide a basis for future electromagnetic applications in medicine. They also reinforce the notion that physical factors acting to influence the electrical condition of living organisms play a key role in biology (Liboff 2009).

Based on the presented data, we could define “well-being” as a condition where a living organism is not just healthy, but moreover, is at an equilibrium state with the natural environment. Since both the natural environment and living organisms are of electric/electromagnetic nature, "wellness" is a condition of subtle electromagnetic equilibrium. If this equilibrium is disrupted by exposure to unnatural EMFs, wellness will be disrupted as well, and if this situation persists health will be impacted sooner or later.

8. CONCLUSIONS

In the present study we attempted to elucidate the fact that the nature of life itself is electromagnetic. Electric oscillations imposed on living organisms by the environmental periodicity due to the terrestrial and lunar motion (circadian, monthly, annual, etc) through the operation of the central circadian biological clock (the SCN in the mammalian brain), play a fundamental role in keeping organisms in resonance with their natural environment. These electrical oscillations manifesting as cell membrane voltage oscillations, or intracellular ionic oscillations, seem to control the operation of the heart, brain, and the rest of bodily organs, and of every single cell. We tried to show the connection these electrical oscillations described previously as intracellular "spontaneous" ionic oscillations, have with the function of the circadian biological clock, and consequently with the periodicity of our natural environment.

External EMFs interact with endogenous physiological ones and can be either beneficial or detrimental for living organisms. External EMFs that generate endogenous currents coherent with physiological ones e.g. during wound healing or bone fracture healing, can be beneficial. These are usually static fields of intensities similar to (or even smaller than) the endogenous physiological ones. On the contrary, external EMFs of varying/alternating nature, modulated and pulsed fields such as those associated with modern wireless telecommunications or produced by power lines, would not be expected to have beneficial action. Rather as demonstrated in the present chapter, these can be expected to be detrimental even at intensities thousands or even millions of times smaller than those of the current exposure limits. Ways of direct and indirect electromagnetic interaction between environmental fields and living systems are described in the present chapter. Perhaps, indirect ways (section 6.2) seem to be more plausible.

Electricity and magnetism are natural powers discovered and used by our civilization. They can be used either for the benefit or to the detriment of life. It is obvious that we cannot use these natural powers without cost. We should then rather use them safely and gently, always being mindful of biological/health consequences for all living creatures and of the integrity of our natural environment. Without this, our technology is useless and meaningless.

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